PCT ORLD INTELLECTUAL PROPERTY ORGANIZA
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : A61K 31/00

A2

(11) International Publication Number: **WO 00/16755**

(43) International Publication Date: 30 March 2000 (30.03.00)

(21) International Application Number: PCT/EP99/06886

(22) International Filing Date: 17 September 1999 (17.09.99)

(30) Priority Data:
9820420.9 18 September 1998 (18.09.98) GB

(71) Applicant *(for all designated States except US)*: GLAXO GROUP LIMITED [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: BROWN, Nathaniel, A. [US/US]; Glaxo Wellcome Inc., Five Moore Drive, Research Triangle Park, NC 27709 (US). CONDREAY, Lynn, D. [US/US]; Glaxo Wellcome Inc., Five Moore Drive, Research Triangle Park, NC 27709 (US). GRAY, Douglas, Fraser [GB/GB]; Glaxo Wellcome plc, 891–995 Greenford Road, Greenford, Middlesex UB6 0HE (GB). RUBIN, Marc [US/US]; Glaxo Wellcome Inc., Five Moore Drive, Research Triangle Park, NC 27709 (US).

(74) Agent: TEUTEN, Andrew, J.; Glaxo Wellcome plc, Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
Without international search report and to be republished upon receipt of that report.

(54) Title: ANTIVIRAL COMBINATIONS

(57) Abstract

The present invention relates to therapeutic combinations comprising (2R, cis) –4–amino–1– (2–hydroxymethyl–1, 3–oxathiolan–5–yl) –pyrimidin–2–one (lamivudine) and a second therapeutic agent selected from (9–[(R) –2–(phosphonomethoxy) ethyl]adenine, (PMEA or adefovir) and bis(pivaloyloxymethyl) (9–[(R) –2– (phosphonomethoxy)ethyl]adenine, (the oral prodrug of PMEA, adefovir dipivoxil) w hich have anti–hepatitis B virus (HBV) activity. The present invention is also concerned with pharmaceutical compositions containing said combinations and their use in the treatment of HBV infections including infections with HBV mutants bearing resistance to nucleoside and/or non–nucleoside inhibitors.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : A61K 31/505, 31/52

A3

(11) International Publication Number: WO 00/16755

(43) International Publicati n Date: 30 March 2000 (30.03.00)

(21) International Application Number: PCT/EP99/06886

(22) International Filing Date: 17 September 1999 (17.09.99)

(30) Priority Data:
9820420.9 18 September 1998 (18.09.98) GB

(71) Applicant *(for all designated States except US)*: GLAXO GROUP LIMITED [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: BROWN, Nathaniel, A. [US/US]; Glaxo Wellcome Inc., Five Moore Drive, Research Triangle Park, NC 27709 (US). CONDREAY, Lynn, D. [US/US]; Glaxo Wellcome Inc., Five Moore Drive, Research Triangle Park, NC 27709 (US). GRAY, Douglas, Fraser [GB/GB]; Glaxo Wellcome plc, 891–995 Greenford Road, Greenford, Middlesex UB6 0HE (GB). RUBIN, Marc [US/US]; Glaxo Wellcome Inc., Five Moore Drive, Research Triangle Park, NC 27709 (US).

(74) Agent: TEUTEN, Andrew, J.; Glaxo Wellcome plc, Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

With international search report.

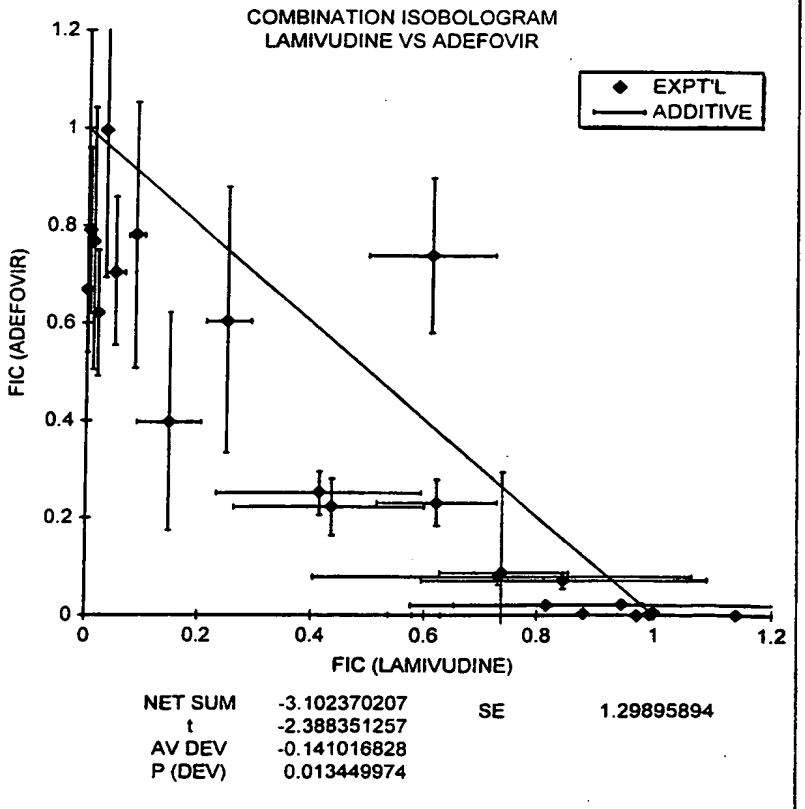
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(88) Date of publication of the international search report:
25 May 2000 (25.05.00)

(54) Title: ANTIVIRAL COMBINATIONS OF LAMIVUDINE AND ADEFOVIR

(57) Abstract

The present invention relates to therapeutic combinations comprising (2R, cis) -4-amino-1- (2-hydroxymethyl-1, 3-oxathiolan-5-yl) -pyrimidin-2-one (lamivudine) and a second therapeutic agent selected from (9-[(R) -2-(phosphonomethoxy) ethyl]adenine, (PMEA or adefovir) and bis(pivaloyloxymethyl) (9-[(R) -2-(phosphonomethoxy)ethyl]adenine, (the oral prodrug of PMEA, adefovir dipivoxil) w hich have anti-hepatitis B virus (HBV) activity. The present invention is also concerned with pharmaceutical compositions containing said combinations and their use in the treatment of HBV infections including infections with HBV mutants bearing resistance to nucleoside and/or non-nucleoside inhibitors.



INTERNATIONAL SEARCH REPORT

ional Application No
PCT/EP 99/06886

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/505 A61K31/52

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	BARTNOF H. S.: "Preveon shows benefits for patients co-infected with HIV and HBV" HIV AND HEPATITIS.COM, 'Online! 18 August 1999 (1999-08-18), XP002132867 Retrieved from the Internet: <URL:http://www.hivandhepatitis.com/hiv/v1 0089904.html> 'retrieved on 2000-03-13! the whole document --- -/--	1-21

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 March 2000	27/03/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Gonzalez Ramon, N

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	PERRILLO: "Gilead Presents Preliminary Clinical Data demostrating activity of adefovir dipivoxil against lamivudine-resistant Hepatitis B virus" GILEAD SCIENCES PRESS RELEASE ARCHIVE, 'Online! 9 April 1999 (1999-04-09), XP002132868 Retrieved from the Internet: <URL:http://www.gilead.com/webpage_templates/frame_home.php3> 'retrieved on 2000-03-13! the whole document	1-21
X,P	THOMPSON M. ET AL: "Randomized Study of Adefovir Dipivoxil (ADV) in combination with Indinavir (IDV) and reverse transcriptase inhibitors for treatment-naive HIV infected patients" ABSTRACTS AND POSTERS IAPAC, 'Online! 8 November 1998 (1998-11-08), XP002132869 Retrieved from the Internet: <URL:http://www.iapac.org/conferences/glasgow98/gileadglasgow5.html> 'retrieved on 2000-03-13! abstract; table 1	1-21
X	ONO-NITA, S. K. (1) ET AL: "Susceptibility of lamivudine resistant hepatitis B virus to other antivirals: Adefovir and lobucavir." HEPATOLOGY, (OCT., 1998) VOL. 28, NO. 4 PART 2, PP. 165A. MEETING INFO.: BIENNIAL SCIENTIFIC MEETING OF THE INTERNATIONAL ASSOCIATION FOR THE STUDY OF THE LIVER AND THE 49TH ANNUAL MEETING AND POSTGRADUATE COURSES OF THE AMERICAN ASSOCIATION FOR THE , XP000890075 abstract	1-21
X	MULATO, A.S. ET AL: "Anti-HIV activity of adefovir (PMEA) and PMPA in combination with antiretroviral compounds: in vitro analyses" ANTIVIRAL RES. (1997), 36(2), 91-97 , XP000890091 abstract; figure 1A page 93, column 2, paragraph 2	1-21

-/--

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SHAW, T. ET AL: "Synergistic inhibition of in vitro hepadnaviral replication by PMEA and penciclovir or lamivudine." ANTIVIRAL RESEARCH, (1997) VOL. 34, NO. 2, PP. A51. MEETING INFO.: MEETING OF THE INTERNATIONAL SOCIETY FOR ANTIVIRAL RESEARCH AND THE TENTH INTERNATIONAL CONFERENCE ON ANTIVIRAL RESEARCH ATLANTA, GEORGIA, USA APRIL 6-11, 1997 , XP000890096 abstract	1-21
P,X	DE CLERCQ E: "Perspectives for the treatment of hepatitis B virus infections." INTERNATIONAL JOURNAL OF ANTIMICROBIAL AGENTS, (1999 JUL) 12 (2) 81-95. REF: 72 , XP000890077 abstract; figure 3 page 92, column 2	1-21
P,X	PESSOA M.G. ET AL: "Update on clinical trials in the treatment of hepatitis B." JOURNAL OF GASTROENTEROLOGY AND HEPATOLOGY, (1999) 14/SUPPL. (S6-S11). , XP000890090 abstract page S10, column 2	1-21
T	PETERS M G ET AL: "Fulminant hepatic failure resulting from lamivudine -resistant hepatitis B virus in a renal transplant recipient: durable response after orthotopic liver transplantation on adefovir dipivoxil and hepatitis B immune globulin." TRANSPLANTATION, (1999 DEC 27) 68 (12) 1912-4. , XP000890081 abstract; table 1	1-21
E	WO 99 66936 A (NOVIRIO PHARMACEUTICALS LIMITE;BRYANT MARTIN L ; MYERS MAUREEN W () 29 December 1999 (1999-12-29) claims 11,12,38	1-22

INTERNATIONAL SEARCH REPORT

[redacted]ation on patent family members

[redacted]onal Application No
PCT/EP 99/06886

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9966936 A	29-12-1999	NONE	

09/787,327

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

To:
GLAXO WELLCOME PLC
Glaxo Wellcome House
Attn. Teuten, Andrew J.
Berkeley Avenue
Greenford
Middlesex UB6 ONN
UNITED KINGDOM

Date of mailing (day/month/year)	27/03/2000
Applicant's or agent's file reference: PU3514/PCT	FOR FURTHER ACTION See paragraphs 1 and 4 below
International application No.: PCT/EP 99/ 06886	International filing date (day/month/year) 17/09/1999
Applicant: GLAXO GROUP LIMITED et al.	

1. [X] The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Claudia Aragone

Form PCT/ISA/220 (July 1998)

Express Mail Label
EL395942155US

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international pbulication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped),whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international appplication is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
PU3514/PCT		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 99/ 06886	17/09/1999	18/09/1998
Applicant		
GLAXO GROUP LIMITED et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established by this Authority to read as follows:

   ANTIVIRAL COMBINATIONS OF LAMIVUDINE AND ADEFOVIR

5. With regard to the **abstract**,

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No. 1

   [ ] as suggested by the applicant.

   [X] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 99/06886

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/505 A61K31/52

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	BARTNOF H. S.: "Preveon shows benefits for patients co-infected with HIV and HBV" HIV AND HEPATITIS.COM, 'Online! 18 August 1999 (1999-08-18), XP002132867 Retrieved from the Internet: <URL:http://www.hivandhepatitis.com/hiv/v1 0089904.html> 'retrieved on 2000-03-13! the whole document --- -/--	1-21

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 March 2000	27/03/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax (+31–70) 340–3016	Gonzalez Ramon, N

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	PERRILLO: "Gilead Presents Preliminary Clinical Data demostrating activity of adefovir dipivoxil against lamivudine-resistant Hepatitis B virus" GILEAD SCIENCES PRESS RELEASE ARCHIVE, 'Online! 9 April 1999 (1999-04-09), XP002132868 Retrieved from the Internet: <URL:http://www.gilead.com/webpage_templates/frame_home.php3> 'retrieved on 2000-03-13! the whole document	1-21
X,P	THOMPSON M. ET AL: "Randomized Study of Adefovir Dipivoxil (ADV) in combination with Indinavir (IDV) and reverse transcriptase inhibitors for treatment-naive HIV infected patients" ABSTRACTS AND POSTERS IAPAC, 'Online! 8 November 1998 (1998-11-08), XP002132869 Retrieved from the Internet: <URL:http://www.iapac.org/conferences/glasgow98/gileadglasgow5.html> 'retrieved on 2000-03-13! abstract; table 1	1-21
X	ONO-NITA, S. K. (1) ET AL: "Susceptibility of lamivudine resistant hepatitis B virus to other antivirals: Adefovir and lobucavir." HEPATOLOGY, (OCT., 1998) VOL. 28, NO. 4 PART 2, PP. 165A. MEETING INFO.: BIENNIAL SCIENTIFIC MEETING OF THE INTERNATIONAL ASSOCIATION FOR THE STUDY OF THE LIVER AND THE 49TH ANNUAL MEETING AND POSTGRADUATE COURSES OF THE AMERICAN ASSOCIATION FOR THE , XP000890075 abstract	1-21
X	MULATO, A.S. ET AL: "Anti-HIV activity of adefovir (PMEA) and PMPA in combination with antiretroviral compounds: in vitro analyses" ANTIVIRAL RES. (1997), 36(2), 91-97 , XP000890091 abstract; figure 1A page 93, column 2, paragraph 2	1-21

-/—

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SHAW, T. ET AL: "Synergistic inhibition of in vitro hepadnaviral replication by PMEA and penciclovir or lamivudine." ANTIVIRAL RESEARCH, (1997) VOL. 34, NO. 2, PP. A51. MEETING INFO.: MEETING OF THE INTERNATIONAL SOCIETY FOR ANTIVIRAL RESEARCH AND THE TENTH INTERNATIONAL CONFERENCE ON ANTIVIRAL RESEARCH ATLANTA, GEORGIA, USA APRIL 6-11, 1997 , XP000890096 abstract	1-21
P,X	DE CLERCQ E: "Perspectives for the treatment of hepatitis B virus infections." INTERNATIONAL JOURNAL OF ANTIMICROBIAL AGENTS, (1999 JUL) 12 (2) 81-95. REF: 72 , XP000890077 abstract; figure 3 page 92, column 2	1-21
P,X	PESSOA M.G. ET AL: "Update on clinical trials in the treatment of hepatitis B." JOURNAL OF GASTROENTEROLOGY AND HEPATOLOGY, (1999) 14/SUPPL. (S6-S11). , XP000890090 abstract page S10, column 2	1-21
T	PETERS M G ET AL: "Fulminant hepatic failure resulting from lamivudine -resistant hepatitis B virus in a renal transplant recipient: durable response after orthotopic liver transplantation on adefovir dipivoxil and hepatitis B immune globulin." TRANSPLANTATION, (1999 DEC 27) 68 (12) 1912-4. , XP000890081 abstract; table 1	1-21
E	WO 99 66936 A (NOVIRIO PHARMACEUTICALS LIMITE;BRYANT MARTIN L ; MYERS MAUREEN W () 29 December 1999 (1999-12-29) claims 11,12,38	1-22

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 99/06886

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9966936 A	29-12-1999	NONE	

PATENT COOPERATION TREATY

Q2

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 12 May 2000 (12.05.00)	
International application No. PCT/EP99/06886	**Applicant's or agent's file reference** PU3514/PCT
International filing date (day/month/year) 17 September 1999 (17.09.99)	**Priority date** (day/month/year) 18 September 1998 (18.09.98)
Applicant BROWN, Nathaniel, A. et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

21 March 2000 (21.03.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Nestor Santesso
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

EPO - DG 1

PCT

REQUEST

17. 09. 1999

(61) International Application No. PCT/EP 99/06886

International Filing Date 17 SEP 1999 (17. 09. 1999)

EUROPEAN PATENT OFFICE
PCT INTERNATIONAL APPLICATION
Name of receiving Office and "PCT International Application"

The undersigned requests that the present International application be processed according to the Patent Cooperation Treaty

Applicant's or agent's file reference *(if desired) (12 characters maximum)* PU3514/PCT

Box No. I TITLE OF INVENTION

Antiviral Combinations

Box No. II APPLICANT

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below).*

Glaxo Group Limited
Glaxo Wellcome House
Berkeley Avenue
Greenford, Middlesex
UB6 0NN, GB

☐ This person is also inventor.

Telephone No. 0171 493 4060

Facsimile No. 0181 966 8838

Teleprinter No. 25456

State *(i.e. country)* of nationality: GB

State *(i.e. country)* of residence: GB

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANTS AND/OR (FURTHER) INVENTORS

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

BROWN, Nathaniel A.
Glaxo Wellcome Inc.
Five Moore Drive
Research Triangle Park
NC 27709
US

This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality: US

State *(i.e. country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country).*

TEUTEN, Andrew J.
Glaxo Wellcome plc
Glaxo Wellcome House, Berkeley Avenue
Greenford, Middlesex
UB6 0NN
GB

Telephone No.: 0171-493-4060

Facsimile No.: 0181-966-8838

Teleprinter No.: 25456

☐ Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to to which correspondence should be sent.

Express Mail Label
EL395942155US

Continuation of Box No. III FURTHER APPLICANTS AND/OR (FURTHER) INVENTORS

If none of the following sub-boxes is used, this sheet is not to be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

CONDREAY, Lynn D.
Glaxo Wellcome Inc.
Five Moore Drive
Research Triangle Park
NC 27709
US

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality: US

State *(i.e. country)* of residence: US

This person is applicant for the purposes of:
- ☐ all designated States
- ☐ all designated States except the United States of America
- ☒ the United States of America only
- ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

GRAY, Douglas Fraser
Glaxo Wellcome plc
891-995 Greenford Road
Greenford, Middlesex,
UB6 0HE
GB

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality: GB

State *(i.e. country)* of residence: GB

This person is applicant for the purposes of:
- ☐ all designated States
- ☐ all designated States except the United States of America
- ☒ the United States of America only
- ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

RUBIN, Marc
Glaxo Wellcome Inc.
Five Moore Drive
Research Triangle Park
NC 27709
US

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality: US

State *(i.e. country)* of residence: US

This person is applicant for the purposes of:
- ☐ all designated States
- ☐ all designated States except the United States of America
- ☒ the United States of America only
- ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality:

State *(i.e. country)* of residence:

This person is applicant for the purposes of:
- ☐ all designated States
- ☐ all designated States except the United States of America
- ☐ the United States of America only
- ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. VI PRIORITY CLAIM ☐ Further priority claims are indicated in the Supplemental Box

Filing Date of Earlier Application (day/month/year)	Number Of earlier application	Where earlier application is: national application: country	regional application:* regional Office	International application: receiving Office
item (1) (18.09.98) 18 September 1998	9820420.9	GB		
item (2)				
item (3)				

☐ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office)* identified above as item(s):_____

** Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earli application was filed (Rue 4.10(b)(ii)). See Supplemental Box.*

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):* ISA/

Request to use results of earlier search; reference to that search *(if an earlier search has been carried out by or requested from the International Searching Authority):* Date *(day/month/year)* Number Country *(or regional office)*

Box. VIII CHECK LIST; LANGUAGE OF FILING

This international application contains the following **number of sheets:**

request	: 4
description (excluding sequence listing part)	: 23
claims	: 3
abstract	: 1
drawings	: 1
sequence listing part of description	:_____
Total number of sheets	: 32

This international application is **accompanied** by the item(s) marked below:

1. ☑ fee calculation sheet
2. ☐ separate signed power of attorney
3. ☐ copy of general power of attorney; reference number, if any:
4. ☐ statement explaining lack of signature
5. ☐ priority document(s) identified in Box No. VI as item(s):
6. ☐ translation of international application into (language):
7. ☐ separate indications concerning deposited microorganism or other biological material
8. ☐ nucleotide and/or amino acid sequence listing in computer readable form
9. ☐ other *(specify):*

Figure of the drawings which should accompany the abstract:

Language of filing of the International application: English

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

Andrew J. TEUTEN
Agent for the Applicants

For receiving Office use only

1. Date of actual receipt of the purported international application: 17. 09. 1999 / 17 SEP 1999
2. Drawings ☒ received: ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:
4. Date of timely receipt of the required corrections under PCT Article 11(2):
5. International Searching Authority specified by the applicant: ISA/
6. ☐ Transmittal of search copy delayed until search fee is paid

For International Bureau use only

Date of receipt of the record copy by the International Bureau

See Notes to the request form

Box No. V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) *(mark the applicable check-boxes; at least one must be marked):*

Regional Patent

☑ **AP** **ARIPO Patent:** **GH** Ghana, **GM** Gambia, **KE** Kenya, **LS** Lesotho, **MW** Malawi, **SD** Sudan, **SZ** Swaziland, **UG** Uganda, **ZW** Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT

☑ **EA** **Eurasian Patent:** **AM** Armenia, **AZ** Azerbaijan, **BY** Belarus, **KG** Kyrgyzstan, **KZ** Kazakstan, **MD** Republic of Moldova, **RU** Russian Federation, **TJ** Tajikistan, **TM** Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT

☑ **EP** **European Patent:** **AT** Austria, **BE** Belgium, **CH and LI** Switzerland and Liechtenstein, **CY** Cyprus, **DE** Germany, **DK** Denmark, **ES** Spain, **FI** Finland, **FR** France, **GB** United Kingdom, **GR** Greece, **IE** Ireland, **IT** Italy, **LU** Luxembourg, **MC** Monaco, **NL** Netherlands, **PT** Portugal, **SE** Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT

☑ **OA** **OAPI Patent:** **BF** Burkina Faso, **BJ** Benin, **CF** Central African Republic, **CG** Congo, **CI** Côte d'Ivoire, **CM** Cameroon, **GA** Gabon, **GN** Guinea, **GW** Guinea Bissau, **ML** Mali, **MR** Mauritania, **NE** Niger, **SN** Senegal, **TD** Chad, **TG** Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)*.....

National Patent *(if other kind of protection or treatment desired, specify on dotted line):*

☑ **AE** United Arab Emirates
☑ **AL** Albania.....
☑ **AM** Armenia.....
☑ **AT** Austria.....
☑ **AU** Australia.....
☑ **AZ** Azerbaijan
☑ **BA** Bosnia and Herzegovina .....
☑ **BB** Barbados
☑ **BG** Bulgaria.....
☑ **BR** Brazil.....
☑ **BY** Belarus.....
☑ **CA** Canada
☑ **CH and LI** Switzerland and Liechtenstein
☑ **CN** China.....
☑ **CU** Cuba.....
☑ **CZ** Czech Republic.....
☑ **DE** Germany.....
☑ **DK** Denmark.....
☑ **EE** Estonia.....
☑ **ES** Spain.....
☑ **FI** Finland.....
☑ **GB** United Kingdom
☑ **GD** Grenada
☑ **GE** Georgia.....
☑ **GH** Ghana.....
☑ **GM** Gambia
☑ **HR** Croatia .....
☑ **HU** Hungary.....
☑ **ID** Indonesia
☑ **IL** Israel.....
☑ **IN** India.....
☑ **IS** Iceland
☑ **JP** Japan.....
☑ **KE** Kenya.....
☑ **KG** Kyrgyzstan.....
☑ **KP** Democratic People's Republic of Korea.....
.....
☑ **KR** Republic of Korea.....
☑ **KZ** Kazakstan.....
☑ **LC** Saint Lucia
☑ **LK** Sri Lanka
☑ **LR** Liberia
☑ **LS** Lesotho.....
☑ **LT** Lithuania
☑ **LU** Luxembourg
☑ **LV** Latvia
☑ **MD** Republic of Moldova.....
☑ **MG** Madagascar.....
☑ **MK** The former Yugoslav Republic of Macedonia
.....
☑ **MN** Mongolia
☑ **MW** Malawi.....
☑ **MX** Mexico.....
☑ **NO** Norway
☑ **NZ** New Zealand.....
☑ **PL** Poland.....
☑ **PT** Portugal.....
☑ **RO** Romania
☑ **RU** Russian Federation.....
☑ **SD** Sudan
☑ **SE** Sweden
☑ **SG** Singapore
☑ **SI** Slovenia.....
☑ **SK** Slovakia.....
☑ **SL** Sierra Leone
☑ **TJ** Tajikistan.....
☑ **TM** Turkmenistan.....
☑ **TR** Turkey.....
☑ **TT** Trinidad and Tobago.....
☑ **UA** Ukraine.....
☑ **UG** Uganda.....
☑ **US** United States of America.....
.....
☑ **UZ** Uzbekistan.....
☑ **VN** Viet Nam.....
☑ **YU** Yugoslavia.....
☑ **ZA** South Africa
☑ **ZW** Zimbabwe

Check-boxes reserved for designating States which have become party to the PCT after issuance of this sheet.

☑ **CR** Costa Rica.....
☑ **DM** Dominica.....
☑ **TZ** Tanzania.....

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation of a designation consists of the filing of a notice specifying that designation and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.)*

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

Teuten, Andrew J.
GLAXO WELLCOME PLC
Glaxo Wellcome House
Berkeley Avenue
Greenford
Middlesex UB6 0NN
GRANDE BRETAGNE

PCT

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	09.10.2000
Applicant's or agent's file reference PU3514/PCT	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP99/06886	17/09/1999	18/09/1998

Applicant
GLAXO GROUP LIMITED et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Oberhauser, A Tel +49 89 2399-8139

Express Mail Label
EL395942155US

TENT COOPERATION TR Y

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
PU3514/PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP99/06886	17/09/1999	18/09/1998
International Patent Classification (IPC) or national classification and IPC A61K31/00		
Applicant GLAXO GROUP LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
21/03/2000	09.10.2000
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Economou, D Telephone No. +49 89 2399 8599

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP99/06886

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

D scription, pages:

1-23 as originally filed

Claims, No.:

1-22 as received on 25/08/2000 with letter of 25/08/2000

Drawings, No.:

1 as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 10-15,18-21.

because:

☒ the said international application, or the said claims Nos. 10-15,18-21 (see separate sheet, item 1) relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-21 (see separate sheet, items 3a and 3b)
	No:	Claims	22 (see separate sheet, item 3c)
Inventive step (IS)	Yes:	Claims	1-9,11,19-21 (see separate sheet, item 3b)
	No:	Claims	10,12-18 (see separate sheet, item 3a)
Industrial applicability (IA)	Yes:	Claims	1-9,16-17,22 (YES; see separate sheet, item 2a); 10-15, 18-21 (see separate sheet, items 1 and 2b)
	No:	Claims	

2. Citations and explanations

see separate sheet

The following IPER is based on th assumption that the present application is fully entitled to its priority date as claimed.

1). Claims 10-15 and 18-21 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

2). a). The subject-matter of claims 1-9, 16-17 and 22 fulfils the requirements of industrial applicability.

b). For the assessment of the present claims 10-15 and 18-21 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

3). a). SHAW, T. ET AL: "Synergistic inhibition of in vitro hepadnaviral replication by PMEA and penciclovir or lamivudine." ANTIVIRAL RESEARCH, (1997) VOL. 34, NO. 2, PP. A51. MEETING INFO.: MEETING OF THE INTERNATIONAL SOCIETY FOR ANTIVIRAL RESEARCH AND THE TENTH INTERNATIONAL CONFERENCE ON ANTIVIRAL RESEARCH ATLANTA, GEORGIA, USA APRIL 6-11, 1997 (=**D1**) discloses synergistic action of a combination of PMEA with lamivudine in ratios of 3:1 and 44:1 (see abstract). In the light of **D1**, the subject-matter of claims 10,12-15, although formally novel since it relates to a treatment of a mammal, does not involve an inventive step since the synergistic action of PMEA with lamivudine is obvious from **D1**.
The same applies also to the subject-matter of claims 16-18 defining combinations of lamivudine with adefovir dipivoxil, since it is known from a further document **D2** (=MULATO, A.S. ET AL: "Anti-HIV activity of adefovir (PMEA) and PMPA in combination with antiretroviral compounds: in vitro analyses" ANTIVIRAL RES. (1997), 36(2), 91-97) that adefovir dipivoxil is a prodrug of adefovir (see abstract)

and mentions that both adefovir as well adefovir dipivoxil are active against hepatitis B virus (see abstract).

b). On the contrary, the subject-matter of claims 1-9,11,and 19-21 is novel and involves also an inventive step, since the claimed synergistic ratio of lamivudine to adefovir or adefovir dipivoxil has neither been disclosed nor rendered obvious in the available prior art.

c). Claims should be defined by technical features (Rule 6.3 PCT). In the case of claim 22 information to the patient does not appear to be a technical feature and hence the subject-matter of said claim discloses nothing more than a pack comprising either lamivudine or adefovir dipivoxil (.."at least one"..). As far as lamivudine is commercially available (Epivir ^{R}) the subject-matter of claim 22 is not novel and a claim directed to a patient pack comprising either lamivudine or adefovir dipivoxil characterised by an insert comprising patient information would be not clear (see above).

Claims

1. A combination comprising (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-pyrimidin-2-one or a pharmaceutically acceptable derivative thereof and a second therapeutic agent, bis(pivaloyloxymethyl)(9-[(R)-2-(phosphonomethoxy)ethyl]adenine or a pharmaceutically acceptable derivative thereof wherein (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-pyrimidin-2-one and the second therapeutic agent are present in the range 40:1 to 1:1 by weight.

2. A combination according to claim 1 wherein the ratio is in the range 25:1 to 15:1 by weight of active ingredients.

3. A combination according to any one of claims 1 to 3 for use in medicine.

4. A pharmaceutical formulation comprising a combination according to any one of claims 1 to 3 in association with one or more pharmaceutically acceptable carriers therefor.

5. A pharmaceutical formulation for use in the treatement of HBV comprising (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-pyrimidin-2-one or a pharmaceutically acceptable derivative thereof and a second therapeutic agent selected from (9-[(R)-2-(phosphonomethoxy)ethyl]adenine or a pharmaceutically acceptable derivative thereof, and bis(pivaloyloxymethyl)(9-[(R)-2-(phosphonomethoxy)ethyl]adenine or a pharmaceutically acceptable derivative thereof wherein (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-pyrimidin-2-one and the second therapeutic agent are present in the range 40:1 to 1:1 by weight.

6. A formulation according to claims 4 or 5 in unit dosage form.

7. A formulation according to any one of claims 4 to 6 suitable for oral administration.

8. A formulation according to any one of claims 5 to 7 comprising between 25 to 150 mg of lamivudine and 5 to 60 mg adefovir dipivoxil.

9. A formulation according to claim 8 comprising 100 mg of lamivudine and 10 mg adefovir dipivoxil.

10. A method for the treatment of a mammal, including a human, with an HBV infection comprising administration of a therapeutically effective amount of a combination comprising (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-pyrimidin-2-one or a pharmaceutically acceptable derivative thereof and a second therapeutic agent selected from (9-[(R)-2-(phosphonomethoxy)ethyl]adenine or a pharmaceutically acceptable derivative thereof, and bis(pivaloyloxymethyl)(9-[(R)-2-(phosphonomethoxy)ethyl]adenine or a pharmaceutically acceptable derivative thereof.

11. A method as claimed in claim 10 wherein the combination is as claimed in any of claims 1 to 3.

12. A method according to claim 10 or claim 11 wherein the combination is administered simultaneously.

13. A method according to claim 10 or claim 11 wherein the combination is administered sequentially.

14. A method according to claim 10 or claim 11 wherein the combination is administered as a single combined formulation.

15. A method as claimed in any one of claims 10 to 14 for the treatment of an HBV infection resistant to nucleoside and/or non-nucleoside inhibitors of the replication of the hepatitis B virus

16. Use of (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-pyrimidin-2-one in the manufacture of a medicament for administration either simultaneously or sequentially with bis(pivaloyloxymethyl)(9-[2-(phosphonomethoxy)ethyl]adenine, for the treatment of an HBV infection.

17. Use of bis(pivaloyloxymethyl)(9-[2-(phosphonomethoxy)ethyl]adenine in the manufacture of a medicament for administration either simultaneously or sequentially with (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one for the treatment of an HBV infection.

18. Use of a combination comprising (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-pyrimidin-2-one or a pharmaceutically acceptable derivative thereof and a second therapeutic agent bis(pivaloyloxymethyl)(9-[(R)-2-(phosphonomethoxy)ethyl]adenine or a pharmaceutically acceptable derivative thereof for the treatment of an HBV infection.

19. Use of a combination as claimed in any one of claims 1 to 3 for the treatment of an HBV infection.

20. Use of a combination comprising (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-pyrimidin-2-one or a pharmaceutically acceptable derivative thereof and a second therapeutic agent selected from either (9-[(R)-2-(phosphonomethoxy)ethyl]adenine or a pharmaceutically acceptable derivative thereof, or bis(pivaloyloxymethyl)(9-[(R)-2-(phosphonomethoxy)ethyl]adenine or a pharmaceutically acceptable derivative thereof wherein (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-pyrimidin-2-one and the second therapeutic agent are present in the range 40:1 to 1:1 by weight, for the treatment of an HBV infection resistant to nucleoside and/or nonnucleoside inhibitor.

21. Use of a combination as claimed in any one of claims 1 to 3 for the treatment of an HBV infection resistant to nucleoside and/or nonnucleoside inhibitor of the replication of the hepatitis B virus.

22. A patient pack comprising of at least one active ingredient selected from (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-pyrimidin-2-one, and bis(pivaloyloxymethyl)(9-[2-(phosphonomethoxy)ethyl]adenine and an information insert containing directions on the use of both active ingredients together in combination.

PATENT COOPERATION TREATY

PCT

15

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
PU3514/PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP99/06886	17/09/1999	18/09/1998
International Patent Classification (IPC) or national classification and IPC A61K31/00		
Applicant GLAXO GROUP LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
21/03/2000	09.10.2000
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Economou, D Telephone No. +49 89 2399 8599

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP99/06886

I. Basis of the r port

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-23	as originally filed			

Claims, No.:

1-22	as received on	25/08/2000	with letter of	25/08/2000

Drawings, No.:

1	as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 10-15,18-21.

because:

☒ the said international application, or the said claims Nos. 10-15,18-21 (see separate sheet, item 1) relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

V. R asoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-21 (see separate sheet, items 3a and 3b)
	No:	Claims	22 (see separate sheet, item 3c)
Inventive step (IS)	Yes:	Claims	1-9,11,19-21 (see separate sheet, item 3b)
	No:	Claims	10,12-18 (see separate sheet, item 3a)
Industrial applicability (IA)	Yes:	Claims	1-9,16-17,22 (YES; see separate sheet, item 2a); 10-15, 18-21 (see separate sheet, items 1 and 2b)
	No:	Claims	

2. Citations and explanations

s e separate sheet

The following IPER is based on the assumption that the present application is fully entitled to its priority date as claimed.

1). Claims 10-15 and 18-21 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

2). a). The subject-matter of claims 1-9, 16-17 and 22 fulfils the requirements of industrial applicability.

b). For the assessment of the present claims 10-15 and 18-21 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

3). a). SHAW, T. ET AL: "Synergistic inhibition of in vitro hepadnaviral replication by PMEA and penciclovir or lamivudine." ANTIVIRAL RESEARCH, (1997) VOL. 34, NO. 2, PP. A51. MEETING INFO.: MEETING OF THE INTERNATIONAL SOCIETY FOR ANTIVIRAL RESEARCH AND THE TENTH INTERNATIONAL CONFERENCE ON ANTIVIRAL RESEARCH ATLANTA, GEORGIA, USA APRIL 6-11, 1997 (=**D1**) discloses synergistic action of a combination of PMEA with lamivudine in ratios of 3:1 and 44:1 (see abstract). In the light of **D1**, the subject-matter of claims 10,12-15, although formally novel since it relates to a treatment of a mammal, does not involve an inventive step since the synergistic action of PMEA with lamivudine is obvious from **D1**.
The same applies also to the subject-matter of claims 16-18 defining combinations of lamivudine with adefovir dipivoxil, since it is known from a further document **D2** (=MULATO, A.S. ET AL: "Anti-HIV activity of adefovir (PMEA) and PMPA in combination with antiretroviral compounds: in vitro analyses" ANTIVIRAL RES. (1997), 36(2), 91-97) that adefovir dipivoxil is a prodrug of adefovir (see abstract)

and mentions that both adefovir as well adefovir dipivoxil are active against hepatitis B virus (see abstract).

b). On the contrary, the subject-matter of claims 1-9,11,and 19-21 is novel and involves also an inventive step, since the claimed synergistic ratio of lamivudine to adefovir or adefovir dipivoxil has neither been disclosed nor rendered obvious in the available prior art.

c). Claims should be defined by technical features (Rule 6.3 PCT). In the case of claim 22 information to the patient does not appear to be a technical feature and hence the subject-matter of said claim discloses nothing more than a pack comprising either lamivudine or adefovir dipivoxil (.."at least one"..). As far as lamivudine is commercially available (Epivir ^{R}) the subject-matter of claim 22 is not novel and a claim directed to a patient pack comprising either lamivudine or adefovir dipivoxil characterised by an insert comprising patient information would be not clear (see above).

Claims

1. A combination comprising (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-pyrimidin-2-one or a pharmaceutically acceptable derivative thereof and a second therapeutic agent selected from (9-[(R)-2-(phosphonomethoxy)ethyl]adenine or a pharmaceutically acceptable derivative thereof, and bis(pivaloyloxymethyl)(9-[(R)-2-(phosphonomethoxy)ethyl]adenine or a pharmaceutically acceptable derivative thereof wherein (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-pyrimidin-2-one and the second therapeutic agent are present in the range 40:1 to 1:1 by weight.

2. A combination according to claim 1 wherein the ratio is in the range 25:1 to 15:1 by weight of active ingredients.

3. A combination according to claim 1 or 2 wherein the second therapeutic agent is bis(pivaloyloxymethyl)(9-[(R)-2-(phosphonomethoxy)ethyl]adenine or a pharmaceutically acceptable derivative thereof.

4. A combination according to any one of claims 1 to 3 for use in medicine.

5. A pharmaceutical formulation comprising a combination according to any one of claims 1 to 3 in association with one or more pharmaceutically acceptable carriers therefor.

6. A formulation according to claim 5 in unit dosage form.

7. A formulation according to any one of claims 5 to 6 suitable for oral administration.

8. A formulation according to any one of claims 5 to 7 comprising between 25 to 150 mg of lamivudine and 5 to 60 mg adefovir dipivoxil.

9. A formulation according to claim 8 comprising 100 mg of lamivudine and 10 mg adefovir dipivoxil.

10. A method for the treatment of a mammal, including a human, with an HBV infection comprising administration of a therapeutically effective amount of a combination comprising (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-pyrimidin-2-one or a pharmaceutically acceptable derivative thereof and a second therapeutic agent selected from (9-[(R)-2-(phosphonomethoxy)ethyl]adenine or a pharmaceutically acceptable derivative thereof, and bis(pivaloyloxymethyl)(9-[(R)-2-(phosphonomethoxy)ethyl]adenine or a pharmaceutically acceptable derivative thereof.

11. A method as claimed in claim 10 wherein the combination is as claimed in any of claims 1 to 3.

12. A method according to claim 10 or claim 11 wherein the combination is administered simultaneously.

13. A method according to claim 10 or claim 11 wherein the combination is administered sequentially.

14. A method according to claim 10 or claim 11 wherein the combination is administered as a single combined formulation.

15. A method as claimed in any one of claims 10 to 14 for the treatment of an HBV infection resistant to nucleoside and/or non-nucleoside inhibitors of the replication of the hepatitis B virus

16. Use of (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-pyrimidin-2-one in the manufacture of a medicament for administration either simultaneously or sequentially with bis(pivaloyloxymethyl)(9-[2-(phosphonomethoxy)ethyl]adenine, for the treatment of an HBV infection.

17. Use of bis(pivaloyloxymethyl)(9-[2-(phosphonomethoxy)ethyl]adenine in the manufacture of a medicament for administration either simultaneously or

sequentially with (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one for the treatment of an HBV infection.

18. Use of a combination comprising (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-pyrimidin-2-one or a pharmaceutically acceptable derivative thereof and a second therapeutic agent selected from (9-[(R)-2-(phosphonomethoxy)ethyl]adenine or a pharmaceutically acceptable derivative thereof, and bis(pivaloyloxymethyl)(9-[(R)-2-(phosphonomethoxy)ethyl]adenine or a pharmaceutically acceptable derivative thereof for the treatment of an HBV infection.

19. Use of a combination as claimed in any one of claims 1 to 3 for the treatment of an HBV infection.

20. Use of a combination comprising (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-pyrimidin-2-one or a pharmaceutically acceptable derivative thereof and a second therapeutic agent selected from either (9-[(R)-2-(phosphonomethoxy)ethyl]adenine or a pharmaceutically acceptable derivative thereof, or bis(pivaloyloxymethyl)(9-[(R)-2-(phosphonomethoxy)ethyl]adenine or a pharmaceutically acceptable derivative thereof for the treatment of an HBV infection resistant to nucleoside and/or nonnucleoside inhibitor.

21. Use of a combination as claimed in any one of claims 1 to 3 for the treatment of an HBV infection resistant to nucleoside and/or nonnucleoside inhibitor of the replication of the hepatitis B virus.

22. A patient pack comprising of at least one active ingredient selected from (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-pyrimidin-2-one, and bis(pivaloyloxymethyl)(9-[2-(phosphonomethoxy)ethyl]adenine and an information insert containing directions on the use of both active ingredients together in combination.

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:
GLAXO WELLCOME PLC
Glaxo Wellcome House
Attn. Teuten, Andrew J.
Berkeley Avenue
Greenford
Middlesex UB6 ONN
UNITED KINGDOM

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference PU3514/PCT	Date of mailing (day/month/year) 27/03/2000
International application No. PCT/EP 99/ 06886	FOR FURTHER ACTION See paragraphs 1 and 4 below
Applicant GLAXO GROUP LIMITED et al.	International filing date (day/month/year) 17/09/1999

1. [X] The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

Within 19 months from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within 20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority dat or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Claudia Aragone

Form PCT/ISA/220 (July 1998)

Express Mail Label
EL395942155US

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international pbulication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped),whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international appplication is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
PU3514/PCT		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 99/ 06886	17/09/1999	18/09/1998
Applicant		
GLAXO GROUP LIMITED et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established by this Authority to read as follows:

   ANTIVIRAL COMBINATIONS OF LAMIVUDINE AND ADEFOVIR

5. With regard to the **abstract**,

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No. 1

   [ ] as suggested by the applicant.

   [X] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 99/06886

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/505 A61K31/52

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	BARTNOF H. S.: "Preveon shows benefits for patients co-infected with HIV and HBV" HIV AND HEPATITIS.COM, 'Online! 18 August 1999 (1999-08-18), XP002132867 Retrieved from the Internet: <URL:http://www.hivandhepatitis.com/hiv/v1 0089904.html> 'retrieved on 2000-03-13! the whole document —— -/—	1-21

intervening prior art published after priority date

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 March 2000	27/03/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Gonzalez Ramon, N

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	PERRILLO: "Gilead Presents Preliminary Clinical Data demostrating activity of adefovir dipivoxil against lamivudine-resistant Hepatitis B virus" GILEAD SCIENCES PRESS RELEASE ARCHIVE, 'Online! 9 April 1999 (1999-04-09), XP002132868 Retrieved from the Internet: <URL:http://www.gilead.com/webpage_templates/frame_home.php3> 'retrieved on 2000-03-13! the whole document	1-21
X,P	THOMPSON M. ET AL: "Randomized Study of Adefovir Dipivoxil (ADV) in combination with Indinavir (IDV) and reverse transcriptase inhibitors for treatment-naive HIV infected patients" ABSTRACTS AND POSTERS IAPAC, 'Online! 8 November 1998 (1998-11-08), XP002132869 Retrieved from the Internet: <URL:http://www.iapac.org/conferences/glasgow98/gileadglasgow5.html> 'retrieved on 2000-03-13! abstract; table 1	1-21
X	ONO-NITA, S. K. (1) ET AL: "Susceptibility of lamivudine resistant hepatitis B virus to other antivirals: Adefovir and lobucavir." HEPATOLOGY, (OCT., 1998) VOL. 28, NO. 4 PART 2, PP. 165A. MEETING INFO.: BIENNIAL SCIENTIFIC MEETING OF THE INTERNATIONAL ASSOCIATION FOR THE STUDY OF THE LIVER AND THE 49TH ANNUAL MEETING AND POSTGRADUATE COURSES OF THE AMERICAN ASSOCIATION FOR THE , XP000890075 abstract	1-21
X	MULATO, A.S. ET AL: "Anti-HIV activity of adefovir (PMEA) and PMPA in combination with antiretroviral compounds: in vitro analyses" ANTIVIRAL RES. (1997), 36(2), 91-97 , XP000890091 abstract; figure 1A page 93, column 2, paragraph 2	1-21

-/--

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 99/06886

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SHAW, T. ET AL: "Synergistic inhibition of in vitro hepadnaviral replication by PMEA and penciclovir or lamivudine." ANTIVIRAL RESEARCH, (1997) VOL. 34, NO. 2, PP. A51. MEETING INFO.: MEETING OF THE INTERNATIONAL SOCIETY FOR ANTIVIRAL RESEARCH AND THE TENTH INTERNATIONAL CONFERENCE ON ANTIVIRAL RESEARCH ATLANTA, GEORGIA, USA APRIL 6-11, 1997 , XP000890096 abstract	1-21
P,X	DE CLERCQ E: "Perspectives for the treatment of hepatitis B virus infections." INTERNATIONAL JOURNAL OF ANTIMICROBIAL AGENTS, (1999 JUL) 12 (2) 81-95. REF: 72 , XP000890077 abstract; figure 3 page 92, column 2	1-21
P,X	PESSOA M.G. ET AL: "Update on clinical trials in the treatment of hepatitis B." JOURNAL OF GASTROENTEROLOGY AND HEPATOLOGY, (1999) 14/SUPPL. (S6-S11). , XP000890090 abstract page S10, column 2	1-21
T	PETERS M G ET AL: "Fulminant hepatic failure resulting from lamivudine -resistant hepatitis B virus in a renal transplant recipient: durable response after orthotopic liver transplantation on adefovir dipivoxil and hepatitis B immune globulin." TRANSPLANTATION, (1999 DEC 27) 68 (12) 1912-4. , XP000890081 abstract; table 1	1-21
E	WO 99 66936 A (NOVIRIO PHARMACEUTICALS LIMITE;BRYANT MARTIN L ; MYERS MAUREEN W () 29 December 1999 (1999-12-29) claims 11,12,38	1-22

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 99/06886

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9966936 A	29-12-1999	NONE	

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Artic 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
PU3514/PCT		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 99/ 06886	17/09/1999	18/09/1998
Applicant		
GLAXO GROUP LIMITED et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established by this Authority to read as follows:

   ANTIVIRAL COMBINATIONS OF LAMIVUDINE AND ADEFOVIR

5. With regard to the **abstract**,

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with th abstract is Figure No. 1

   [ ] as suggested by the applicant.

   [X] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.